REMARKS

Claims 1-20 were previously cancelled. Claims 21-29 remain pending. No new claims amendments are presented at this time. Rather, reconsideration of the application is requested in view of the remarks which follow.

Turning to the Office Action, claims 21-29 stand rejected under 35 USC §112, 1st paragraph, on the grounds of enablement. The Office Action expressly acknowledges that the specification is enabling for the FLC-4 cell line. However, the position is taken that enablement is lacking for "any and all human hepatocytes" (Office Action at page 2).

The rejection is traversed. It is respectfully submitted that the present claims are fully enabled for at least the following reasons.

In assessing the enablement issue, the Examiner points to Aoki et al. and Aizaki et al. as being representative of the state of the prior art (Office Action at page 3). In doing so, the Examiner considers that HCV cannot be proliferated in a human hepatocyte other than FLC4 cells.

Applicant respectfully disagrees.

Attention is directed to Seipp et al., cited by the Examiner in connection with the Office Action mailed on May 4, 2005. Seipp et al. show that HCV proliferates in HuH7 and HepG2 (although the amount of proliferated HCV is quite low in the system provided by Seipp).

Further, there is no teaching in Aoki that HCV cannot proliferate in any human hepatocyte other than FLC4 cell lines. Rather, Aoki shows in Figs. 5 and 6 that the expression of pT7HCVLuc is observed not only in FLC4 cells but also in HepG2 cells and Huh7 cells. In addition, HCV actually proliferates in living human liver. The skilled artisan would therefore readily understand that HCV could proliferate in any

human hepatocyte and could practice the full scope of the invention without undue experimentation.

At the same time, it is clear that FLC4 cells are more effective cells for the expression of pT7HCVLuc in Aoki et al., and it is also suitable to propagate HCV in the present invention. That is consistent with the statements made by the Examiner in discussing Aoki and Aizaki (Office Action at page 3). There is no teaching in Aizaki that HCV does not proliferate in hepatocytes other than FLC4 cells.

In view of the foregoing, it is respectfully submitted that the present application fully meets the enablement requirement of 35 USC §112, 1st paragraph. Reconsideration and withdrawal of the rejection are therefore requested.

Claims 21-29 stand rejected under 35 USC §103(a) over Kawada, Nagamori et al. (1998) and Aoki et al. (1998).

The rejection is traversed. The cited documents, even in combination, fail to teach or suggest the features of the present invention and cannot therefore sustain the rejection.

The present invention is directed to a method for proliferating HCV by using a radial flow bioreactor. The proliferation of HCV in the immobilized human hepatocytes under the continuous stream of a liquid culture medium can produce a significant amount of HCV (of almost 10^5) and the production is quite stable for 100 days by which time even HCV proteins can be detected (see page 22, part (5) of Example 1, page 27, part (2) of Example 2 and Fig. 4 of the present application).

Kawada et al. disclose the radial flow bioreactor itself and FLC4 cells proliferate in the reactor. Kawada et al. do not, however, teach or suggest that HCV can proliferate in the immobilized FLC4 cells under the continuous stream of a liquid culture medium in the reactor and that propagation of HCV in the radial flow bioreactor under the continuous stream of a liquid culture medium gives quite a number of HCV of

10^5, which is far beyond that of the prior art such as Seipp et al., as discussed previously.

Aoki et al. cannot remedy the deficiencies of Kawada. Aoki et al. disclose that pT7HCVLuc is more suitably expressed in the transfected FLC4 cells than HepG2 or Huh7 cells. One skilled in the art would not, however, presume on the basis of Aoki et al. that HCV proliferates in FLC4 cells up to 10^5 because Aoki et al. shows not the proliferation of HCV, but merely the expression of a marker protein of luciferase by co-transfection with AdexCAT7 (Fig.1) and pT7HCVLuc (Fig.3).

Since the system including the co-transfection with recombinant plasmids used in Aoki et al. is designed for the expression of heterologous marker protein under the conventional culture conditions, in view of Aoki et al., one skilled in the art would not expect that the propagation of HCV in the radial flow bioreactor under the continuous stream of a liquid culture medium would give 10^5 of HCV stably for 100 days.

Thus, the present invention has a remarkable effect which is unexpected even for the skilled artisan. Such surprisingly excellent results further rebut any case of *prima facie* obviousness to be contended.

Accordingly, the aforementioned rejection is properly withdrawn.

It is well-known that to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference(s) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaec*k, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP § 2143.

There is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the cited references to make the claimed invention, nor is there a reasonable expectation of success.

In view of the above remarks, Applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

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